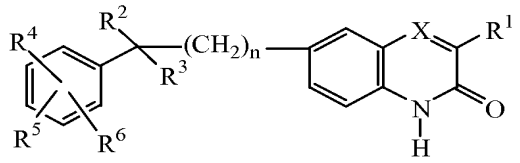
CLAIMS

1. A compound of formula (I),



(I)

the *N*-oxide forms, the addition salts and the stereo-chemically isomeric forms thereof, wherein

n is 0, 1 or 2;

X is N or CR^7, wherein R^7 is hydrogen or taken together with R^1 may form a bivalent radical of formula -CH=CH-CH=CH-;

R^1 is C_{1-6}alkyl or thiophenyl;

R^2 is hydrogen, hydroxy, C_{1-6}alkyl, C_{3-6}alkynyl or taken together with R^3 may form =O;

R^3 is a radical selected from

$-(CH_2)_s-NR^8R^9$	(a-1),
-O-H	(a-2),
$-O-R^{10}$	(a-3),
$-S-R^{11}$	(a-4), or
—C≡N	(a-5),

wherein

s is 0, 1, 2 or 3;

R^8, R^{10} and R^{11} are each independently selected from –CHO, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, piperidinylC_{1-6}alkylaminocarbonyl, piperidinyl, piperidinylC_{1-6}alkyl, piperidinylC_{1-6}alkylaminocarbonyl, C_{1-6}alkyloxy, thiophenylC_{1-6}alkyl, pyrrolylC_{1-6}alkyl, arylC_{1-6}alkylpiperidinyl, arylcarbonylC_{1-6}alkyl, arylcarbonylpiperidinylC_{1-6}alkyl, haloindozolylpiperidinylC_{1-6}alkyl, arylC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, and

R^9 is hydrogen or C_{1-6}alkyl;

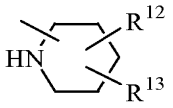
or R^3 is a group of formula

$-(CH_2)_t-Z$ (b-1),

wherein

t is 0, 1, 2 or 3;

-Z is a heterocyclic ring system selected from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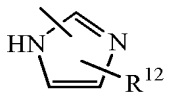
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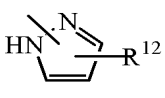
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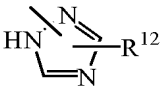
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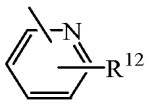
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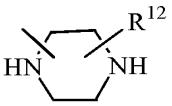
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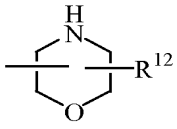
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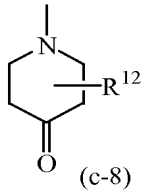
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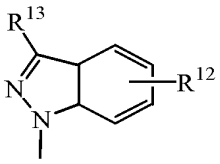
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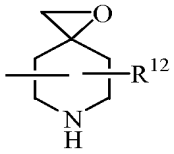
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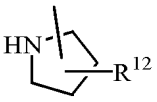
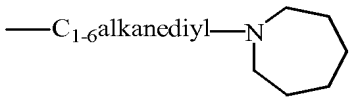
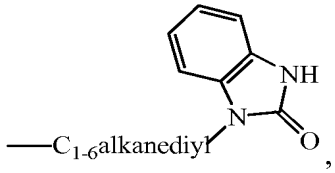

(c-11)

wherein R^{12} is hydrogen, halo, C_{1-6}alkyl, aminocarbonyl, amino, hydroxy, aryl,


, 
,

C_{1-6}alkylaminoC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkylamino, arylC_{1-6}alkyl, di(phenylC_{2-6}alkenyl), piperidinyl, piperidinylC_{1-6}alkyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkylC_{1-6}alkyl, aryloxy(hydroxy)C_{1-6}alkyl, haloindazolyl, arylC_{1-6}alkyl, arylC_{2-6}alkenyl, arylC_{1-6}alkylamino, morpholino, C_{1-6}alkylimidazolyl, pyridinylC_{1-6}alkylamino; and

R^{13} is hydrogen, piperidinyl or aryl;

R^4, R^5 and R^6 are each independently selected from hydrogen, halo, trihalomethyl, trihalomethoxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, aminoC_{1-6}alkyl, di(C_{1-6}alkyl)amino, di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy or C_{1-6}alkyloxycarbonyl, or C_{1-6}alkyl substituted with 1, 2 or 3 substituents independently selected from hydroxy, C_{1-6}alkyloxy, or aminoC_{1-6}alkyloxy; or

when R^5 and R^6 are on adjacent positions they may taken together form a bivalent radical of formula

-O-CH_2-O (d-1),

-O-$(CH_2)_2$-O- (d-2),

-CH=CH-CH=CH- (d-3), or

-NH-C(O)-NR^{14}=CH- (d-4),

wherein R^{14} is C_{1-6}alkyl;

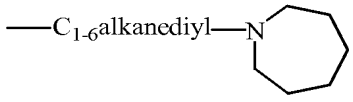
aryl is phenyl, phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy;

with the proviso that when

n is 0, X is N, R^1 is C_{1-6}alkyl, R^2 is hydrogen, R^3 is a group of formula (b-1), t is 0, -Z is the heterocyclic ring system (c-2) wherein said heterocyclic ring system -Z is attached to the rest of the molecule with a nitrogen atom, and R^{12} is hydrogen or C_{1-6}alkyl; then

at least one of the substituents R^4, R^5 or R^6 is other than hydrogen, halo, C_{1-6}alkyloxy and trihalomethyl.

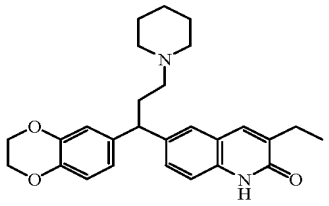
2. A compound as claimed in claim 1 wherein

R^1 is C_{1-6}alkyl; R^3 is a radical selected from (a-1), (a-2), (a-3) or (a-5) or is a group of formula (b-1); s is 0, 1 or 2; R^8 and R^{10} are each independently selected from –CHO, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, piperidinylC_{1-6}alkyl, piperidinylC_{1-6}alkylaminocarbonyl, C_{1-6}alkyloxy, thiophenylC_{1-6}alkyl, pyrrolylC_{1-6}alkyl, arylC_{1-6}alkylpiperidinyl, arylcarbonylC_{1-6}alkyl, arylcarbonylpiperidinylC_{1-6}alkyl, haloindozolylpiperidinylC_{1-6}alkyl, or arylC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl; t is 0 or 2; -Z is a heterocyclic ring system selected from (c-1), (c-2), (c-4), (c-6), (c-8), (c-9), or (c-11); R^{12} is hydrogen, C_{1-6}alkyl, aminocarbonyl, 

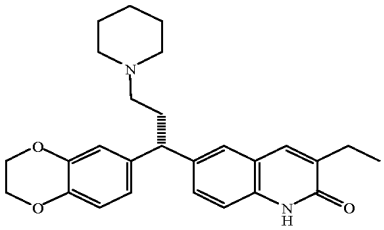
, C_{1-6}alkyloxyC_{1-6}alkylamino, di(phenylC_{2-6}alkenyl), piperidinylC_{1-6}alkyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkylC_{1-6}alkyl, haloindazolyl, or arylC_{2-6}alkenyl; R^4, R^5 and R^6 are each independently selected from hydrogen, halo, trihalomethyl, trihalomethoxy, C_{1-6}alkyl, C_{1-6}alkyloxy, di(C_{1-6}alkyl)amino, di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy or C_{1-6}alkyloxycarbonyl; and when R^5 and R^6 are on adjacent positions they may taken together form a bivalent radical of formula (d-1) or (d-2).

3. A compound according to claim 1 and 2 wherein n is 0; X is CH; R^1 is C_{1-6}alkyl; R^2 is hydrogen; R^3 is a group of formula (b-1); t is 2; -Z is a heterocyclic ring system selected from (c-1); R^{12} is hydrogen; R^{13} is hydrogen; and R^5 and R^6 are on adjacent positions and taken together form a bivalent radical of formula (d-2).

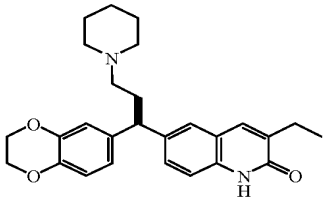
4. A compound according to claim 1, 2 and 3 wherein the compound is compounds No 16, compound No 144, and compound No. 145.



compound 16

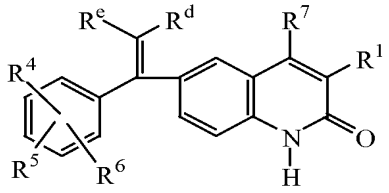


Compound 144



Compound 145

5. A compound of formula (VII-a),



(VII-a)

the *N*-oxide forms, the addition salts and the stereo-chemically isomeric forms thereof, wherein

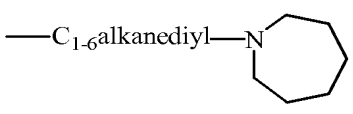
R^1, R^4, R^5, R^6, R^7 and aryl are as defined in claim 1;

R^e is hydrogen or taken together with R^d may form a bivalent radical of formula

$-(CH_2)_2-NR^{15}-(CH_2)_2-$ (e-1), or

$-CH_2-NR^{16}-(CH_2)_3-$ (e-2),

wherein R^{15} and R^{16} are each independently selected from hydrogen, C_{1-6}alkyl,



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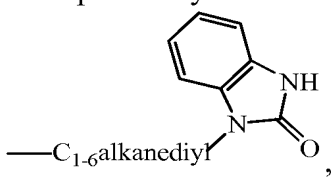


, C_{1-6}alkyloxyC_{1-6}alkyl,

piperidinylC_{1-6}alkyl, C_{3-10}cycloalkylC_{1-6}alkyl, aryloxy(hydroxy)C_{1-6}alkyl, arylC_{1-6}alkyl, or arylC_{2-6}alkenyl; or

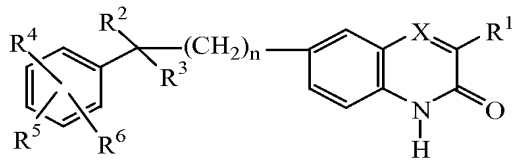
R^d is di(C_{1-6}alkyl)aminoC_{1-6}alkyl or piperidinylC_{1-6}alkyl.

6. A compound as claimed in any of claims 1 to 5 for use as a medicine.

7. A pharmaceutical composition comprising pharmaceutically acceptable carriers and as an active ingredient a therapeutically effective amount of a compound as claimed in claim 1 to 5.

8. A process of preparing a pharmaceutical composition as claimed in claim 7 wherein the pharmaceutically acceptable carriers and a compound as claimed in claim 1 to 5 are intimately mixed.

9. Use of a compound for the manufacture of a medicament for the treatment of a PARP mediated disorder, wherein said compound is a compound of formula (I)



(I)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

n is 0, 1 or 2;

X is N or CR^7, wherein R^7 is hydrogen or taken together with R^1 may form a bivalent radical of formula -CH=CH-CH=CH-;

R^1 is C_{1-6}alkyl or thiophenyl;

R^2 is hydrogen, hydroxy, C_{1-6}alkyl, C_{3-6}alkynyl or taken together with R^3 may form =O;

R^3 is a radical selected from

$-(CH_2)_s-NR^8R^9$ (a-1),

-O-H (a-2),

$-O-R^{10}$ (a-3),

$-S-R^{11}$ (a-4), or

$-C\equiv N$ (a-5),

wherein

s is 0, 1, 2 or 3;

R^8, R^{10} and R^{11} are each independently selected from –CHO, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, piperidinylC_{1-6}alkylaminocarbonyl, piperidinyl, piperidinylC_{1-6}alkyl, piperidinylC_{1-6}alkylaminocarbonyl, C_{1-6}alkyloxy, thiophenylC_{1-6}alkyl, pyrrolylC_{1-6}alkyl, arylC_{1-6}alkylpiperidinyl, arylcarbonylC_{1-6}alkyl, arylcarbonylpiperidinylC_{1-6}alkyl, haloindozolylpiperidinylC_{1-6}alkyl, arylC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, and

R^9 is hydrogen or C_{1-6}alkyl;

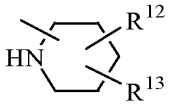
or R^3 is a group of formula

$-(CH_2)_t-Z$ (b-1),

wherein

t is 0, 1, 2 or 3;

-Z is a heterocyclic ring system selected from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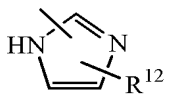
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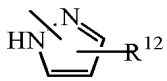
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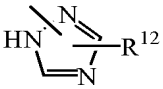
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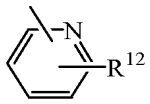
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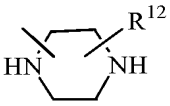
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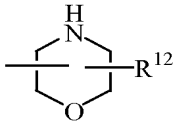
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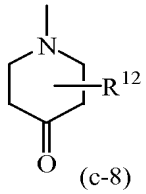
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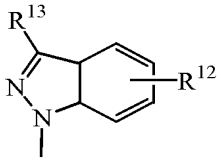
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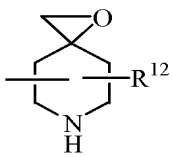
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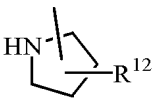
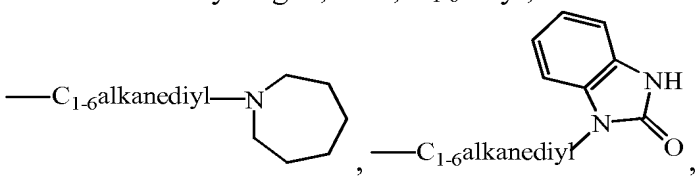

(c-11)

wherein R^{12} is hydrogen, halo, C_{1-6}alkyl, aminocarbonyl, amino, hydroxy, aryl,



C_{1-6}alkylaminoC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkylamino, arylC_{1-6}alkyl, di(phenylC_{2-6}alkenyl), piperidinyl, piperidinylC_{1-6}alkyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkylC_{1-6}alkyl, aryloxy(hydroxy)C_{1-6}alkyl, haloindazolyl, arylC_{1-6}alkyl, arylC_{2-6}alkenyl, arylC_{1-6}alkylamino, morpholino, C_{1-6}alkylimidazolyl, pyridinylC_{1-6}alkylamino; and

R^{13} is hydrogen, piperidinyl or aryl;

R^4, R^5 and R^6 are each independently selected from hydrogen, halo, trihalomethyl, trihalomethoxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, aminoC_{1-6}alkyl, di(C_{1-6}alkyl)amino, di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy or C_{1-6}alkyloxycarbonyl, or C_{1-6}alkyl substituted with 1, 2 or 3 substituents independently selected from hydroxy, C_{1-6}alkyloxy, or aminoC_{1-6}alkyloxy; or

when R^5 and R^6 are on adjacent positions they may taken together form a bivalent radical of formula

-O-CH_2-O	(d-1),
-O-$(CH_2)_2$-O-	(d-2),
-CH=CH-CH=CH-	(d-3), or
-NH-C(O)-NR^{14}=CH-	(d-4),

wherein R^{14} is C_{1-6}alkyl;

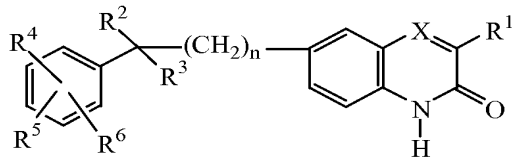
aryl is phenyl, phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy.

10. Use of a compound according to claim 5 for the manufacture of a medicament for the treatment of a PARP mediated disorder.

11. Use according to claim 9 and 10 wherein the treatment involves chemosensitization.

12. Use according to claims 9 and 10 wherein the treatment involves radiosensitization.

13. A combination of a compound with a chemotherapeutic agent wherein said compound is a compound of formula (I)



(I)

the *N*-oxide forms, the pharmaceutically acceptable addition salts and the stereochemically isomeric forms thereof, wherein

n is 0, 1 or 2;

X is N or CR^7, wherein R^7 is hydrogen or taken together with R^1 may form a bivalent radical of formula -CH=CH-CH=CH-;

R^1 is C_{1-6}alkyl or thiophenyl;

R^2 is hydrogen, hydroxy, C_{1-6}alkyl, C_{3-6}alkynyl or taken together with R^3 may form =O;

R^3 is a radical selected from

$-(CH_2)_s-NR^8R^9$ (a-1),
-O-H (a-2),
$-O-R^{10}$ (a-3),
$-S-R^{11}$ (a-4), or
—C≡N (a-5),

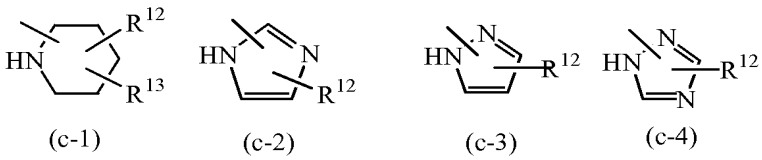
wherein
s is 0, 1, 2 or 3;
R^8, R^{10} and R^{11} are each independently selected from –CHO, C_{1-6}alkyl, hydroxyC_{1-6}alkyl, C_{1-6}alkylcarbonyl, amino, C_{1-6}alkylamino, di(C_{1-6}alkyl)aminoC_{1-6}alkyl, C_{1-6}alkyloxycarbonyl, C_{1-6}alkylcarbonylaminoC_{1-6}alkyl, piperidinylC_{1-6}alkylaminocarbonyl, piperidinyl, piperidinylC_{1-6}alkyl, piperidinylC_{1-6}alkylaminocarbonyl, C_{1-6}alkyloxy, thiophenylC_{1-6}alkyl, pyrrolylC_{1-6}alkyl, arylC_{1-6}alkylpiperidinyl, arylcarbonylC_{1-6}alkyl, arylcarbonylpiperidinylC_{1-6}alkyl, haloindozolylpiperidinylC_{1-6}alkyl, arylC_{1-6}alkyl(C_{1-6}alkyl)aminoC_{1-6}alkyl, and
R^9 is hydrogen or C_{1-6}alkyl;

or R^3 is a group of formula

$-(CH_2)_t-Z$ (b-1),

wherein
t is 0, 1, 2 or 3;

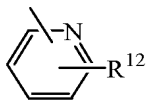
-Z is a heterocyclic ring system selected from

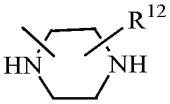

(c-1)

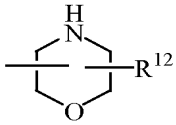
(c-2)

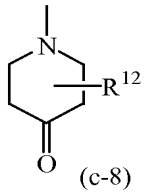
(c-3)

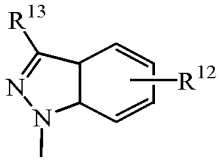
(c-4)

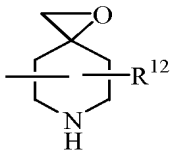

(c-5)

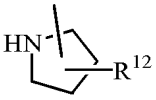

(c-6)


(c-7)

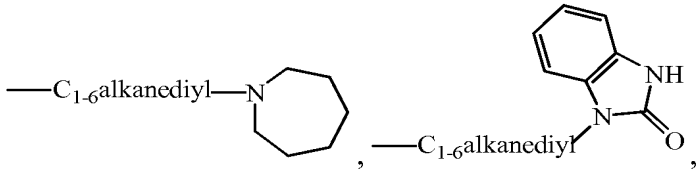

(c-8)


(c-9)


(c-10)


(c-11)

wherein R^{12} is hydrogen, halo, C_{1-6}alkyl, aminocarbonyl, amino, hydroxy, aryl,



C_{1-6}alkylaminoC_{1-6}alkyloxy, C_{1-6}alkyloxyC_{1-6}alkyl, C_{1-6}alkyloxyC_{1-6}alkylamino, arylC_{1-6}alkyl, di(phenylC_{2-6}alkenyl), piperidinyl, piperidinylC_{1-6}alkyl, C_{3-10}cycloalkyl, C_{3-10}cycloalkylC_{1-6}alkyl, aryloxy(hydroxy)C_{1-6}alkyl, haloindazolyl, arylC_{1-6}alkyl, arylC_{2-6}alkenyl, arylC_{1-6}alkylamino, morpholino, C_{1-6}alkylimidazolyl, pyridinylC_{1-6}alkylamino; and

R^{13} is hydrogen, piperidinyl or aryl;

R^4, R^5 and R^6 are each independently selected from hydrogen, halo, trihalomethyl, trihalomethoxy, C_{1-6}alkyl, C_{1-6}alkyloxy, amino, aminoC_{1-6}alkyl, di(C_{1-6}alkyl)amino, di(C_{1-6}alkyl)aminoC_{1-6}alkyloxy or C_{1-6}alkyloxycarbonyl, or C_{1-6}alkyl substituted with 1, 2 or 3 substituents independently selected from hydroxy, C_{1-6}alkyloxy, or aminoC_{1-6}alkyloxy; or

when R^5 and R^6 are on adjacent positions they may taken together form a bivalent radical of formula

-O-CH_2-O (d-1),
-O-$(CH_2)_2$-O- (d-2),
-CH=CH-CH=CH- (d-3), or
-NH-C(O)-NR^{14}=CH- (d-4),

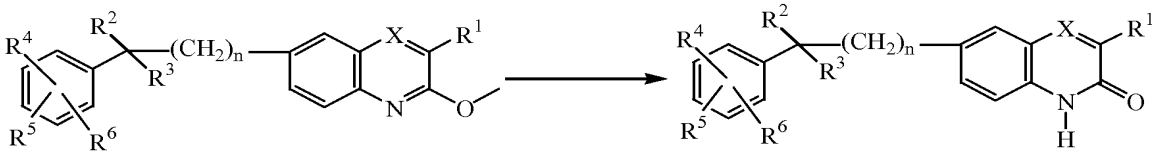
wherein R^{14} is C_{1-6}alkyl;

aryl is phenyl, phenyl substituted with halo, C_{1-6}alkyl or C_{1-6}alkyloxy.

14. A combination of a compound according to claim 5 with a chemotherapeutic agent.

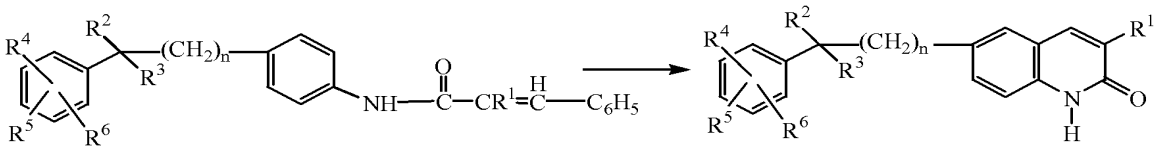
15. A process for preparing a compound as claimed in claim 1 or claim 5, characterized by

a) the hydrolysis of intermediates of formula (VIII), according to art-known methods, by submitting the intermediates of formula (VIII) to appropriate reagents, such as, tinchloride, acetic acid and hydrochloric acid, in the presence of a reaction inert solvent, e.g. tetrahydrofuran,



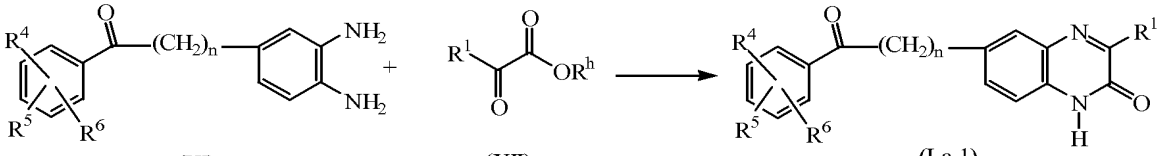
(VIII) (I)

b) the cyclization of intermediates of formula (X), according to art-known cyclizing procedures into compounds of formula (I) wherein X is CH herein referred to as compounds of formula (I-j), preferably in the presence of a suitable Lewis Acid, e.g. aluminum chloride either neat or in a suitable solvent such as, for example, an aromatic hydrocarbon, e.g. benzene, chlorobenzene, methylbenzene and the like; halogenated hydrocarbons, e.g. trichloromethane, tetrachloromethane and the like; an ether, e.g. tetrahydrofuran, 1,4-dioxane and the like or mixtures of such solvents,



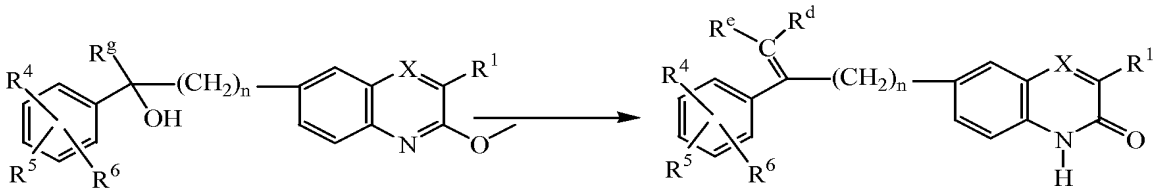
(X) (I-j)

c) the condensation of an appropriate ortho-benzenediamine of formula (XI) with an ester of formula (XII) into compounds of formula (I), wherein X is N and R^2 taken together with R^3 forms =O, herein referred to as compounds of formula (I-a-1), in the presence of a carboxylic acid, e.g. acetic acid and the like, a mineral acid such as, for example hydrochloric acid, sulfuric acid, or a sulfonic acid such as, for example, methanesulfonic acid, benzenesulfonic acid, 4-methylbenzenesulfonic acid and the like,



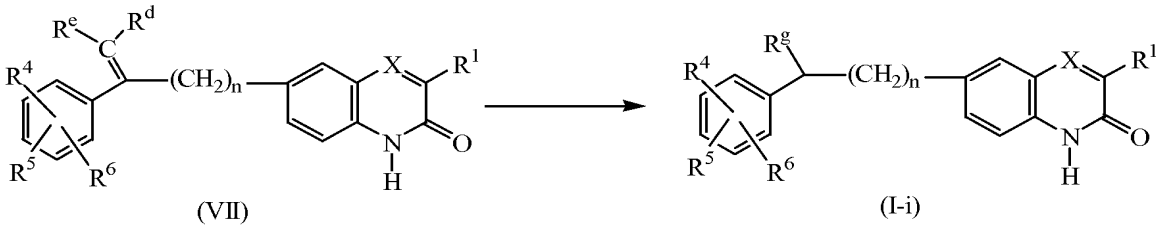
(XI) (XII) (I-a-1)

d) hydrolysing intermediates of formula (VI), wherein R^3 is a group of formula (b-1) or a radical of formula (a-1) wherein s is other than 0, herein referred to as R^g, according to art-known methods, such as stirring the intermediate (VI) in an aqueous acid solution in the presence of a reaction inert solvent with the formation of intermediates and compounds of formula (VII), wherein R^d and R^e are appropriate radicals or taken together with the carbon to which they are attached, form an appropriate heterocyclic ring system as defined in –Z,



(VI) (VII)

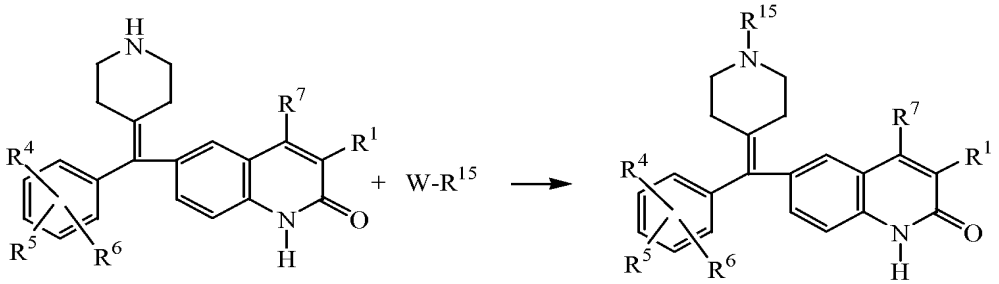
e) converting intermediates of formula (VII), by a selective hydrogenation of said intermediate with an appropriate reducing agent and an appropriate reductant in a suitable solvent with the formation of compounds of formula (I) wherein R^2 is hydrogen and R^g is as defined above, herein referred to as compounds of formula (I-i).



(VII) (I-i)

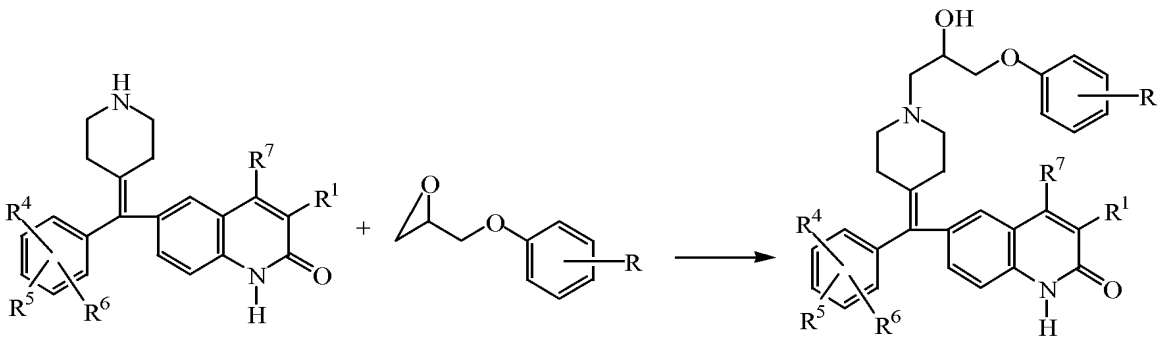
16. A process for preparing a compound as claimed in claim 5, characterized by

a) reacting a compound of formula (VII-a), wherein R^e taken together with R^d forms a bivalent radical of formula (e-1) or (e-2) (e.g. a bivalent radical of formula (e-1)) and R^{15} or R^{16} (e.g. R^{15}) are hydrogen, herein referred to as compounds of formula (VII-a-2), with an intermediate of formula (XIX) wherein W is an appropriate leaving group such as, for example, chloro, bromo, methanesulfonyloxy or benzenesulfonyloxy and R^{15} or R^{16} (e.g. R^{15}) are other than hydrogen, with the formation of compounds of formula (VII-a-1), defined as compounds of formula (VII-a), wherein R^e taken together with R^d forms a bivalent radical of formula (e-1) or (e-2) (e.g. a bivalent radical of formula (e-1)) and R^{15} or R^{16} (e.g. R^{15}) are other than hydrogen, in a reaction-inert solvent; or



(VII-a-2) (XIX) (VII-a-1)

b) reacting a compound of formula (VII-a-2) with an intermediate of formula (XX) wherein R is an appropriate substituent whit the formation of compounds of formula (VII-a) wherein R^{15} or R^{16} (e.g. R^{15}) are aryloxy(hydroxy)C_{1-6}alkyl, herein referred to as compounds of formula (VII-a-3), in the presence of 2-propanol.



(VII-a-2) (XX) (VII-a-3)

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